

**Translation**

**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>30599P WO</b>	<b>FOR FURTHER ACTION</b>	See Form PCT/IPEA/416
International application No. <b>PCT/EP2004/006315</b>	International filing date (day/month/year) <b>11.06.2004</b>	Priority date (day/month/year) <b>11.06.2003</b>
International Patent Classification (IPC) or national classification and IPC		
Applicant <b>CELARES GMBH</b>		

<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>8</u> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> (sent to the applicant and to the International Bureau) a total of <u>6</u> sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>
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Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

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Box No. I

## Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language \_\_\_\_\_ which is the language of a translation furnished for the purposes of:
- ☐ international search (Rule 12.3 and 23.1(b))
- ☐ publication of the international application (Rule 12.4)
- ☐ international preliminary examination (Rule 55.2 and/or 55.3)
2. With regard to the elements of the international application, this report is based on (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):
- ☐ the international application as originally filed/furnished
- ☒ the description:
- pages 1-45 \_\_\_\_\_ as originally filed/furnished
- pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☒ the claims:
- nos. \_\_\_\_\_ as originally filed/furnished
- nos.\* \_\_\_\_\_ as amended (together with any statement) under Article 19
- nos.\* 1-18 \_\_\_\_\_ received by this Authority on 24.03.2005 with letter of 24.03.2005
- nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☒ the drawings:
- sheets 1/5-5/5 \_\_\_\_\_ as originally filed/furnished
- sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, nos. \_\_\_\_\_
- ☐ the drawings, sheets/figs \_\_\_\_\_
- ☐ the sequence listing (specify): \_\_\_\_\_
- ☐ any table(s) related to sequence listing (specify): \_\_\_\_\_
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, nos. \_\_\_\_\_
- ☐ the drawings, sheets/figs \_\_\_\_\_
- ☐ the sequence listing (specify): \_\_\_\_\_
- ☐ any table(s) related to sequence listing (specify): \_\_\_\_\_

\* If item 4 applies, some or all of those sheets may be marked "superseded."

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application
- ☒ claims Nos. 1 (in part) - 6 (in part)

because:

- ☐ the said international application, or the said claims Nos. \_\_\_\_\_  
relate to the following subject matter which does not require an international preliminary examination (*specify*):

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_\_\_\_  
are so unclear that no meaningful opinion could be formed (*specify*):

- ☒ the claims, or said claims Nos. 1 (in part) - 6 (in part) are so inadequately supported  
by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for said claims Nos. 1 (in part) - 6 (in part)

- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished☐ does not comply with the standard

the computer readable form

☐ has not been furnished☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- ☒ See Supplemental Box for further details.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
<b>1. Statement</b>			
Novelty (N)	Claims	1-18	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-18	NO
Industrial applicability (IA)	Claims	1-18	YES
	Claims		NO
<b>2. Citations and explanations (Rule 70.7)</b>			
<p>The new set of claims submitted with the letter of 24 March 2005 is restricted to compounds (Ia) and (Ib), which contain at least two groups of formula (II) consisting of at least three alkylene oxide units (<math>n = 3</math>).</p>			
<p><b>D12:</b> US 2002 010 7224</p>			
<p><b>D16:</b> WO 01/12154</p>			
<p><b>D17:</b> I. Ugi et al., Angew. Chem., 112, 3300-3344 (2000) (cited in the application)</p>			
<p><b>D19:</b> US 6 355 726</p>			
<p><b>D20:</b> EP 1 104 677 (cited in the application)</p>			
<p>1. <u>Novelty (PCT Article 33(2))</u></p>			
<p>Document <b>D12</b> describes compounds containing NH-CO-CH<sub>2</sub>-N-CO (Ia) as a backbone element (compound 12, page 39, example 34), i.e. two polyoxyalkylene groups, of which only one consists of three alkylene oxide units (see compound 12, page 39 or example 34). These compounds can be used to induce an immune response to cancer and HIV.</p>			
<p>Document <b>D16</b> discloses dicarboxylic acid amine compounds of formula (XIV) (B3, page 32, and B17, page 41), which are</p>			

Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement

used as starting materials to produce lipid particles with a targeting function. None of the compounds described contain a polyalkylene oxide unit.

The four-component condensation reaction carried out by Ugi is described in documents **D17**, **D19** and **D20** together with its use for the creation of substance libraries. **D17** discloses compounds of formula (Ia) (page 3315) and formula (Ib) (page 3309. **D19** describes compounds of formula (Ia) (examples 1, 3, 6, 7, 9 and 11). **D20** describes protein conjugates containing a structural element of formula (Ia) and therapeutic and/or diagnostic uses thereof (claims 6 and 8). However, none of the compounds described in these documents contain a polyalkylene oxide unit.

None of the above-cited documents disclose compound (I) or compound (XIV) with two groups of formula (II) where  $n = 3$ . The subject matter of claims 1 to 18 is therefore considered novel.

2. Inventive step (PCT Article 33(3))

The prior art describes compounds of formulas (Ia) and/or (Ib) without two polyoxyalkylene groups consisting of three alkylene oxide units as reagents for modifying biopharmaceuticals. The present application addresses the problem of producing new compounds. Only one substance was tested, namely substance 21. The compounds of formula (Ia) in the present application (formula (II) being the same as formula (IIa) where  $R_1 = \text{OMe}$  and  $n = 3$ ) therefore solve the technical problem of interest. If a person skilled in the art would be unable to predict that with the minor

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Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement

structural modification compared with **D12** (see compound 12, page 39, or example 34, paragraph 35, page 4) compound 21 would retain its biopharmaceutical activity, or if an unexpected effect was observed, then not all the claimed compounds can be regarded as solving the technical problem (the differences are more numerous). Only compounds which are structurally closely related to the compound that has been tested can be regarded as solving the problem, namely compounds of formula (I) containing at least two polyoxyalkylene groups of formula (IIa) where  $R_1 = \text{OMe}$ .

The subject matter of claims 1 to 18 therefore does not involve an inventive step.

## Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

**Box III****Non-establishment of opinion with regard to novelty,  
inventive step and industrial applicability**

- 3.1 Compounds 18, 20 and 22 contain a peroxy group  $O-(OC_2H_4)_{10}$ . This appears to be incorrect because the application relates to compounds containing polyoxyalkylene groups (PCT Rule 91.1).
- 3.2 As a result of the restrictions made, the new set of claims specifies only compounds (Ia) and (Ib), in which radicals V, W, X and Z together have at least two groups of formula (II) consisting of at least three alkylene oxide units. This means that compounds 8, 9, 10, 12 and 14 to 16 in examples 1 to 3, 5 and 7 are not covered by the new claim 1. However, compound 16 was the only substance that was tested in the original application, and must now be regarded as a comparative example. This creates a problem of clarity with respect to the desired scope of protection (PCT Article 6).
- 3.3 According to the applicant, the backbone element of the claimed compounds is  $NH-CO-CW_2$ , a bonding group and at least two polyoxyalkylene groups consisting of at least three alkylene oxide units. However, this is only true when formula (II) is the preferred formula (IIa) (page 10). Otherwise formula (II) contains optional substitutions with OH, OR, COR or hydrocarbons, which may contain heteroatoms. The bonding group is defined in

## Supplemental Box

claim 2, and comprises all possible functional groups. Therefore the current claims 1 to 6 still relate to an inordinately large number of possible compounds (Ia), (Ib) and (XIV), of which only a small proportion are supported by the description in accordance with PCT Article 6 and/or can be regarded as having been disclosed in the application in accordance with PCT Article 5 (only when formula (II) = formula (IIa), where  $R_1 = \text{OMe}$ ,  $n = 3$  and only one tested compound, namely substance 21; see the problems referred to above in points 3.1 and 3.2). In this instance the claims lack the proper support and the application lacks the requisite disclosure to such an extent that it appears impossible to carry out a meaningful search covering the full range of subject matter for which protection is sought. The search was therefore directed to the parts of the claims that appear to be supported and disclosed in the above sense, that is the parts relating to the compounds specified in the exemplary embodiments, including closely related homologous compounds, namely:

For claim 1:  $\text{Ak-O-}[\text{CH}_2\text{-CH}_2\text{-O}]_{0-20}\text{-CH}_2\text{-CH}_2\text{-N}[\text{CO-C}]$   
[G-CO-NH-CH<sub>2</sub>-C] where G = CH<sub>2</sub> or  
C(Me)<sub>2</sub>; full search

For claim 6:  $\text{CH} \dots \text{CH}_2\text{-CH}_2\text{-CH}[(\text{CH})_{0-11}\text{-CO-N}]_2$   
where ... represents a double or triple  
bond; incomplete search.